Evaluation of Pimobendan and N-Terminal Probrain Natriuretic Peptide in the Treatment of Pulmonary Hypertension Secondary to Degenerative Mitral Valve Disease in Dogs


Background: Pimobendan is a positive inotropic and vasodilator that may be useful in the treatment of pulmonary hypertension (PHT) secondary to degenerative mitral valve disease.

Hypothesis: Pimobendan decreases the severity of PHT measured echocardiographically and improves quality-of-life scores. Changes in N-terminal probrain natriuretic peptide (NT-proBNP) concentrations will reflect improvement in severity of PHT.

Animals: Ten client-owned dogs with peak tricuspid regurgitant flow velocity (TRFV) ≥ 3.5 m/s.

Methods: Prospective short-term, double-blinded, crossover design, with a long-term, open-label component. Short term, dogs were randomly allocated to receive either placebo or pimobendan (0.18–0.3 mg/kg PO q12 h) for 14 days. After a 1-week washout, they received the alternative treatment for 14 days, followed by pimobendan open-label for 8 weeks.

Results: Short-term comparison: peak TRFV decreased in all dogs on pimobendan compared with placebo from a median of 4.80 (range, 3.2–5.6) to 3.75 (range, 2.4–4.8) m/s (P < .0001). NT-proBNP concentration decreased after treatment with pimobendan from a median of 2.143 (range, 450–3,981) to 1.329 (range, 123–2,411) pmol/L (P = .0009). All dogs improved their quality-of-life score (P = .006). In the long-term comparisons, peak TRFV decreased in all dogs from a median of 4.28 (range, 3.5–5.7) to 3.52 (range, 2.4–5.0) m/s (P < .0001). No significant changes in NT-proBNP or quality-of-life scores were detected.

Conclusions and Clinical Importance: Pimobendan lowered severity of measurable PHT, improved quality-of-life scores, and decreased NT-proBNP concentrations short-term. Long term, only the reduction in TRFV was maintained.

Key words: Cardiovascular; Echocardiography; Heart failure; Hemodynamics.

Pulmonary hypertension (PHT) is defined as an increase in pulmonary arterial pressure (PAP). Systolic PAP > 30 mmHg or mean PAP > 20 mmHg confirms the diagnosis of PHT.1–9 Three mechanisms may contribute to increased PAP: increased left atrial (LA) pressure, increased pulmonary blood flow, and increased pulmonary vascular resistance. Pulmonary venous hypertension, also termed postcapillary PHT, reflects increased PAP secondary to passive increases in LA pressure. Although idiopathic PHT is common in humans, PHT in dogs is usually associated with an underlying abnormality such as congenital cardiac disease, left heart failure, chronic pulmonary disease, heartworm infestation, or pulmonary thromboembolic disease.1,2,9,10

Brain natriuretic peptides are hormones produced in response to states of circulating volume overload, and act as antagonists of the renin-angiotensin system. In healthy humans and dogs, circulating forms of BNP are derived primarily from the atria, but under pathological conditions, production of BNP increases substantially in both the atria and ventricles.11–13 Cleavage of the prohormone brain natriuretic peptide produces an amino-terminal fragment denoted amino terminal probrain natriuretic peptide (NT-proBNP), and a carboxy-terminal end comprising active BNP.11,13 Numerous diseases that result in right heart dysfunction in humans are associated with increased NT-proBNP concentrations.14,15 Veterinary studies have demonstrated the utility of NT-proBNP concentrations in distinguishing animals with heart disease from normal animals and those with primary respiratory disease.16–18 Additionally, recent information suggests dogs with PHT have NT-proBNP concentrations that are significantly increased compared with dogs with solely primary respiratory disease.19

Pimobendanb is an oral inotropic drug with phosphodiesterase 3 (PDE3) inhibitory and calcium sensitizing effects. Left heart catheterization studies in normal dogs...
and dogs with heart failure have documented that pimobendan caused a marked decrease in left ventricular (LV) end-diastolic pressure and pulmonary capillary wedge pressure.\textsuperscript{19–22} Additionally, pimobendan caused potent vasodilatation of the systemic vasculature in dogs.\textsuperscript{21,22} However, the effect of pimobendan on canine pulmonary vasculature has not been reported. Case reports in humans receiving pimobendan showed promising results in the therapy of primary PHT, in PHT secondary to chronic emphysema, and in a patient with dilated cardiomyopathy and chronic obstructive pulmonary disease.\textsuperscript{23–27}

Effective treatment of severe PHT is difficult, because many of the underlying causes of PHT are progressive and result in irreversible changes in the pulmonary vasculature. Identification and treatment of the underlying cause (eg, closure of left-to-right shunt, treatment of heartworm disease) is optimal. Common symptomatic therapies utilized include oxygen treatment, bronchodilators, vasodilators, and diuretics.\textsuperscript{4} Sildenafil, a PDE5 inhibitor, has been used to treat dogs with PHT, and is regarded as a standard of care in veterinary medicine.\textsuperscript{26,28} In 1 retrospective study, sildenafil did not significantly lower measurable PHT, but did result in clinical improvement.\textsuperscript{29} Pimobendan has been advocated as a therapy for dogs with PHT, but its use has not been critically examined.\textsuperscript{30}

The purpose of this study was to describe the clinical outcome and change in the severity of PHT in dogs with myxomatous mitral valve disease (MVD) treated with pimobendan.

**Materials and Methods**

**Study Animals**

Client-owned dogs with naturally occurring, moderate-to-severe PHT that presented to the University of Missouri, Veterinary Medical Teaching Hospital between May 2006 and September 2007 were eligible. Dogs with a tricuspid regurgitation (TR) jet yielding a peak tricuspid regurgitant flow velocity (TRFV) $\geq 3.5$ m/s were considered candidates. The presence of pulmonic stenosis was exclusionary. Other exclusionary criteria included evidence of any systemic disorder such as renal or hepatic disease likely to have prevented completion of the protocol or to have interfered with metabolism of medication. Additionally, dogs with renal disease and azotemia have been shown to have increased NT-proBNP concentrations.\textsuperscript{31} Dogs were heartworm antigen negative and receiving heartworm medication. Additionally, dogs with renal disease and azotemia have been shown to have increased NT-proBNP concentrations.\textsuperscript{31} Dogs were heartworm antigen negative and receiving heartworm prophylaxis. Pre-existing therapy with cardiac medications was allowed, excluding other PDE inhibitors (eg, theophylline or sildenafil). Dogs in heart failure were stabilized before enrollment.

Nine normal dogs were recruited to serve as negative controls for comparison of NT-proBNP concentrations. Control dogs had normal physical and echocardiographic examinations.

**Study Design**

The study was conducted as a short-term, placebo-controlled, double-blinded, randomized, crossover design, with a long-term, open-label component. Dogs were assigned to initial therapy by a random assignment table. Dogs were enrolled with informed client consent, and the study was approved by the Animal Care and Use Committee at the University of Missouri.

The dogs were examined on days 0, 14, 21, 35, and 91. In the 35-day short-term treatment period, dogs were randomly allocated to receive either placebo or pimobendan (mean dose, 0.25 mg/kg; range, 0.18–0.30 mg/kg) PO q12h for 14 days. Owners were instructed to give the treatment 1 hour before, or 2 hours after feeding. Owners and the investigator performing the echocardiograms were blinded to the group assignment. All measurements were repeated after 14 days, and again after a 1-week washout (day 21). Dogs then received the alternative treatment for 14 days, and measurements were repeated on day 35. After the 35-day crossover period, all dogs received pimobendan for 8 weeks, and all variables were measured on day 91.

**Echocardiography**

A single echosonographer performed all examinations (KJA). Two-dimensional, M-mode, and Doppler echocardiographic examinations were performed utilizing standard views in unsedated dogs.\textsuperscript{32} Three to 5 measurements were averaged for each variable. A peak TRFV $\geq 3.5$ m/s, which is equivalent to a peak TR pressure gradient $\geq 50$ mmHg by the modified Bernoulli equation ($\Delta P = 4 \times v^2$) was considered indicative of moderate to severe PHT. Pulmonary velocity flow profiles were obtained by pulsed-wave Doppler, with the sampling gate positioned at the pulmonic valve. Systolic time intervals were obtained for pulmonary velocity acceleration and ejection time by a simultaneously recorded electrocardiograph (ECG), and were not corrected for heart rate.\textsuperscript{33,34}

**Clinical Evaluation**

Heart rate, rectal temperature, respiratory rate, and body weight were recorded. A standard 6-lead ECG was obtained to determine the underlying rhythm, assess for arrhythmias, and calculate the mean electrical axis.\textsuperscript{35} Thoracic radiographs were obtained at each visit, and a board-certified radiologist provided additional comments on the pulmonary parenchyma. Vertebral heart size scoring was measured using a reference range of 8.5–10.5.\textsuperscript{36} Thoracic radiographs were assigned a pulmonary edema score graded as follows: 1—no edema, 2—mild interstitial density, 3—moderate interstitial density, 4—alveolar pattern, and 5—severe consolidation.\textsuperscript{37} Indirect systolic blood pressure was determined as the mean of 3 readings with an ultrasonic Doppler flow detector. The quality-of-life scoring system (functional evaluation of cardiac health [FETCH] questionnaire) was completed by the owner at each visit.\textsuperscript{38}

**Hematologic Evaluation**

Serum biochemistry profiles were performed by the University of Missouri’s Veterinary Medical Diagnostic Laboratory. For measurement of NT-proBNP, blood was placed into chilled-EDTA collection tubes. Within 20 minutes of collection, the blood was centrifuged for 5 minutes at 1,720 $\times$ g and the supernatant frozen at $-80^\circ$ C. Samples were batched for analysis and submitted frozen on dry ice to the testing laboratory for assay, by previously described methodology.\textsuperscript{17}

**Statistical Analysis**

All calculations and statistical analyses were performed with standard commercial software.\textsuperscript{3,6} Because of the small number of study subjects, values are presented as median and range. Results during the short-term phase were analyzed by a 2-period crossover design, with factors treatment, treatment sequence, and (random) dog. To ensure that treatment order did not affect the short-term results, the analysis first tested for a significant sequence effect. Treatment order was not significant, and therefore the effect of pimobendan therapy was assessed next by the appropriate $F$-test and corresponding $P$-value. Comparison of baseline to day 91 results was performed by the Wilcoxon signed-rank test. The Mann-Whitney rank-sum test
was used for comparisons between the PHT and control group. $P$ values < .05 were considered significant.

**Results**

Thirteen dogs met the study inclusion criteria. One dog withdrew from the study because of the owner relocating, and was excluded from analysis. One dog died between days 35 and 91, and was analyzed only in the short-term cross-over segment of the study. There were too few dogs ($n = 2$) with precapillary PHT to permit statistical analysis, and therefore these dogs were excluded from analysis. However, a brief report of their results is provided for descriptive purposes. The remaining 10 dogs all had chronic degenerative mitral valve disease and were receiving therapy for heart failure.

Six dogs were spayed females and 4 were castrated males. Breeds included Shetland Sheepdog ($n = 2$), Boston Terrier ($n = 1$), Cocker Spaniel ($n = 1$), Bull Terrier ($n = 1$), Dalmatian ($n = 1$), Papillon ($n = 1$), Chihuahua ($n = 1$), Terrier mix ($n = 1$), and Labrador mix ($n = 1$). The median age was 12.8 years (range, 8–14.9 years); median weight was 11.1 kg (range, 4.7–27.5 kg). Clinical signs included cough ($n = 10$), collapse or syncope ($n = 8$), respiratory distress ($n = 3$), and ascites ($n = 2$). Necropsies were not obtained in any dog.

Medications administered during the study period included furosemide ($n = 10$), enalapril ($n = 9$), spironolactone ($n = 3$), hydrocortone ($n = 3$), omega-3 fatty acid/fish oil supplementation ($n = 2$), benazepril ($n = 1$), diltiazem ($n = 1$), digoxin ($n = 1$), flutacsone propionate ($n = 1$), carprofen ($n = 1$), deroxocib ($n = 1$), thryoxine ($n = 1$), taurine ($n = 1$), carnitine ($n = 1$), metronidazole ($n = 1$), and dan shen ($n = 1$). The minimum effective dosage of furosemide was prescribed at all times and re-evaluated at each visit. Two dogs demonstrated clinical and radiographic evidence of progressive heart failure on days 14 and 35, necessitating increases in furosemide dosage at both visits. No changes in treatment with any other cardiac drugs were permitted with 1 exception. Because of recurring diarrhea, 1 dog had digoxin discontinued and the diltiazem dosage increased during the open-label period. No owners reported complications associated with pimobendan.

The characteristics of 9 normal control dogs were compared with the baseline of the 10 dogs with PHT. Control subjects were significantly younger (median, 5 years; range, 0.5–7 years; $P < .0001$), and heavier (median, 19.8 kg; range, 13.8–32.4 kg; $P = .02$) compared with dogs with PHT. The baseline NT-proBNP concentration in patients with PHT (median, 1,799 pmol/L; range, 289–3,723 pmol/L) was significantly higher than that of control dogs (median, 373 pmol/L; range, 209–738 pmol/L; $P = .0013$).

All dogs showed a decrease in peak TRFV while receiving pimobendan treatment (median, 3.75 m/s; range, 2.4–4.8 m/s) compared with placebo (median, 4.4 m/s; range, 3.2–5.6 m/s) in the short-term cross-over phase of the study ($P < .0001$). Peak TRFV also decreased significantly in all dogs from day 0 (median, 4.28 m/s; range, 3.5–5.7 m/s) to day 91 (median, 3.52; range, 2.4–5.0; $P < .0001$; Fig 1).

The summed quality-of-life scores varied widely among patients, with a lower score indicating the owner’s perception of a better quality of life. All dogs experienced a decrease in their summed quality-of-life score on pimobendan (median, 15; range, 1–35) compared with placebo (median, 25.5; range, 2–49; $P = .006$). However, no significant change in the quality-of-life score was found when comparing baseline (median, 22; range, 3–58) to day 91 (median, 17; range, 1–41; $P = .13$; Fig 2).

Concentrations of NT-proBNP decreased significantly with pimobendan therapy (median, 1,329 pmol/L; range, 123–2,411 pmol/L) compared with placebo (median, 2,143 pmol/L; range, 450–3,981 pmol/L; $P = .0009$). However, no significant changes in NT-proBNP concentrations were found in the long-term comparison between baseline (median, 1,799; range, 289–3,723 pmol/L) and day 91 (median, 984 pmol/L; range, 489–3,526 pmol/L; $P = .12$; Fig 3).

Results for selected physical examination, echocardiographic, and hematologic findings were compared for the short-term phase (Table 1) and between baseline and day 91 (Table 2). The only significant change in physical examination findings was a decrease in heart rate with pimobendan treatment compared with placebo ($P = .04$). Therapy with pimobendan resulted in significant improvement in some of the echocardiographic parameters of systolic function and markers of preload. In the short-term phase, the LV internal dimension in systole ($P < .001$), LV dimension in diastole ($P = .01$), and the LV shortening area ($P = .02$) improved. In the long-term comparison, the LV internal dimension in systole ($P = .02$) and the LV shortening area ($P = .04$) remained significantly decreased. There were no significant alterations in the LA dimension or LA to aortic root ratio at any time. There were no changes in the Doppler-derived systolic time intervals of pulmonary artery flow during the
increasing severity of signs. See Figure 1 for explanation of box plots. Values indicate minimal clinical signs, and higher values indicate increased severity of signs. See Figure 1 for explanation of box plots.

There was no significant change long term (*P = .11). Low values indicate minimal clinical signs, and higher values indicate increasing severity of signs. See Figure 1 for explanation of box plots.

short-term phase. However, there were small but significant increases in the pulmonary artery acceleration and ejection times at day 91. There was no significant change in the pulmonary edema score at any time. The VHS decreased significantly with pimobendan therapy during the short-term phase (*P = .003), but this was not maintained long term (P = .26). There was no significant change in the mean electrical axis or discernable abnormal rhythm development with pimobendan therapy.

Nine of the PHT dogs had died or were euthanized after completing the study. One dog was still alive at the time of manuscript submission. The median survival was 352 days (range, 101 to > 874 days).

Two dogs had PHT attributed to pulmonary disease; both were spayed females (a 13.7-year-old West Highland White Terrier and a 12.4-year-old Boston Terrier). Because of the low number of cases, these dogs were excluded from statistical analysis. Their long-term (day 0 versus 91) response to pimobendan is provided briefly for descriptive purposes. In 1 dog, TRFV decreased from 4.0 to 3.9 m/s, NT-proBNP decreased from 661 to 508 pmol/L, and quality-of-life score remained unchanged at 41. In the other dog, TRFV increased from 4.2 to 4.6 m/s, NT-proBNP increased from 1,635 to 2,272 pmol/L, and quality-of-life score increased from 24 to 45.

Discussion

In this study of dogs with naturally occurring, moderate-to-severe PHT secondary to degenerative mitral valve disease, pimobendan therapy was well tolerated when added to standard congestive heart failure therapy. This supports previous studies demonstrating a positive effect of pimobendan in mitral valve disease.

Peak TRFV was the sole determinant used to diagnose PHT echocardiographically in this study. Optimal parallel alignment with the peak tricuspid regurgitant jet requires skill and is vital for accuracy, as is patient cooperation.110 This method allows rapid, noninvasive estimation of pulmonary pressure, through application of the modified Bernoulli equation. In the absence of pulmonic stenosis, the right ventricular to right atrial pressure gradient, when added to the clinically estimated right atrial pressure, can be used to estimate PAP. However, because of certain limitations of the Bernoulli equation, peak TRFV alone was used for statistical analysis. The calculated pressure gradient ignores initial flow velocity, the contribution of flow acceleration, and viscous friction.40 Furthermore, because the Bernoulli equation transforms the data by squaring the flow velocity and multiplying it by 4, there is the potential to magnify small, nonsignificant changes and alter conclusions about the efficacy of treatment. Baseline TRFV was higher than would be expected in these dogs if the increase was solely because of passive increases in LA pressure. However, an increase in pulmonary vascular resistance may accompany long-standing increases in LA pressure, producing a mixed hemodynamic response.5,6,41

The therapeutic benefits of pimobendan for PHT are hypothesized to be because of pulmonary vasodilatation, decreased LA filling pressures, peripheral vasodilatation, and increased right and left ventricular contractility. The improvements seen in the echocardiographic measures of contractility were predictable with the use of a positive inotrope. An inotropically mediated reduction in left ventricular end-diastolic pressure potentially could have accounted for the decrease in TRFV seen in this study. The effect of pimobendan on pulmonary vascular resistance cannot be determined with the model used. Invasive studies utilizing right heart catheterization may clarify whether pimobendan therapy causes pulmonary vasodilatation in dogs, or whether it solely improves ventricular contractility and thereby decreases LA pressure.

The NT-proBNP concentrations in dogs with PHT were increased above those of the healthy control dog population. This result is similar to what has been seen previously in other studies.a,16–18,42 Although NT-proBNP concentrations decreased significantly during the short-term phase, however, there were small but significant increases in the pulmonary artery acceleration and ejection times at day 91. There was no significant change in the pulmonary edema score at any time. The VHS decreased significantly with pimobendan therapy during the short-term phase (*P = .003), but this was not maintained long term (P = .26). There was no significant change in the mean electrical axis or discernable abnormal rhythm development with pimobendan therapy.

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The NT-proBNP concentrations in dogs with PHT were increased above those of the healthy control dog population. This result is similar to what has been seen previously in other studies.a,16–18,42 Although NT-proBNP concentrations decreased significantly during the
short-term phase, this effect was not maintained long
term. This result differs from those of human studies in
which changes in pulmonary hemodynamics paralleled
changes in NT-proBNP.43 The lack of significant results
potentially may be explained by the small study popula-
tion, day-to-day variation in NT-proBNP concentrations
(known to exist in dogs44 and humans45), or possibly pro-
gression of the underlying disease process.

An improvement in quality-of-life score as assessed by
the owner was seen in the short-term comparison, but not
in the long-term phase. Despite this, all owners opted to
continue therapy with pimobendan after conclusion of

Table 1. Comparison of selected physical and diagnostic test results in the short-term comparison while receiving
either a placebo or pimobendan therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Pimobendan</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>133.5 (100–176)</td>
<td>125.5 (99–148)</td>
<td>.04*</td>
</tr>
<tr>
<td>Respiratory rate (rpm)</td>
<td>30 (16–59)</td>
<td>28 (24–59)</td>
<td>.52</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>113.8 (80–147)</td>
<td>113.3 (77–132)</td>
<td>.29</td>
</tr>
<tr>
<td>Vertebral heart size</td>
<td>12.4 (11.2–13.0)</td>
<td>12.2 (11.0–13.0)</td>
<td>.003*</td>
</tr>
<tr>
<td>Mean electrical axis (degrees)</td>
<td>76 (48–161)</td>
<td>82.5 (55–239)</td>
<td>.23</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>34 (16–56)</td>
<td>31 (18–70)</td>
<td>.95</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1 (0.9–2.0)</td>
<td>1.1 (0.8–1.6)</td>
<td>.29</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>49.5 (33–277)</td>
<td>37 (18–244)</td>
<td>.43</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>88.5 (19–955)</td>
<td>143 (15–950)</td>
<td>.75</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.2 (0.1–0.4)</td>
<td>0.2 (0.1–0.5)</td>
<td>.54</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>47 (36–56)</td>
<td>45.5 (39–61)</td>
<td>.43</td>
</tr>
<tr>
<td>PA acceleration time (ms)</td>
<td>47 (27–105)</td>
<td>46 (30–101)</td>
<td>.62</td>
</tr>
<tr>
<td>PA ejection time (ms)</td>
<td>147 (112–298)</td>
<td>142 (92–337)</td>
<td>.79</td>
</tr>
<tr>
<td>PA acceleration time/ejection</td>
<td>0.31 (0.23–0.34)</td>
<td>0.33 (0.20–0.40)</td>
<td>.46</td>
</tr>
<tr>
<td>Left atrial diameter (cm)</td>
<td>2.82 (1.77–4.9)</td>
<td>2.58 (2.14–4.81)</td>
<td>.15</td>
</tr>
<tr>
<td>Left atrial diameter/aortic root</td>
<td>1.90 (1.19–2.57)</td>
<td>1.71 (1.28–2.40)</td>
<td>.31</td>
</tr>
<tr>
<td>LV diastolic diameter (cm)</td>
<td>3.56 (2.47–6.75)</td>
<td>3.36 (1.87–6.23)</td>
<td>.01*</td>
</tr>
<tr>
<td>LV systolic diameter (cm)</td>
<td>1.64 (1.29–4.33)</td>
<td>1.38 (0.63–3.97)</td>
<td>&lt;.001*</td>
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<td>Fractional shortening (%)</td>
<td>48.1 (33.2–61.8)</td>
<td>54.1 (29.8–67.2)</td>
<td>.051</td>
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<tr>
<td>LV shortening area (%)</td>
<td>62.8 (46.3–76.6)</td>
<td>65.8 (47.0–81.3)</td>
<td>.02*</td>
</tr>
</tbody>
</table>

Values presented as median (range).
*P < .05 significant.
LV, left ventricular; PA, pulmonary artery.

Table 2. Comparison of selected physical and diagnostic test results in the long-term comparison between day 0
(before pimobendan therapy) and day 91 (after pimobendan therapy).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 0</th>
<th>Day 91</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>131 (86–176)</td>
<td>128 (95–191)</td>
<td>.86</td>
</tr>
<tr>
<td>Respiratory rate (rpm)</td>
<td>24 (20–59)</td>
<td>28 (24–59)</td>
<td>.67</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>110.7 (85–131)</td>
<td>115.7 (77–144)</td>
<td>.31</td>
</tr>
<tr>
<td>Vertebral heart size</td>
<td>12 (11.2–13)</td>
<td>12.4 (11.2–13)</td>
<td>.26</td>
</tr>
<tr>
<td>Mean electrical axis (degrees)</td>
<td>84 (54–263)</td>
<td>82 (57–260)</td>
<td>.95</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>36 (11–60)</td>
<td>33 (23–98)</td>
<td>.64</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.0 (0.9–1.6)</td>
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<td>.76</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>70 (21–179)</td>
<td>55 (25–246)</td>
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</tr>
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<td>129 (15–1209)</td>
<td>.11</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.2 (0.1–0.3)</td>
<td>0.2 (0.1–0.4)</td>
<td>.58</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>46 (31–56)</td>
<td>44 (41–57)</td>
<td>.81</td>
</tr>
<tr>
<td>PA acceleration time (ms)</td>
<td>39.4 (29–53.2)</td>
<td>43.6 (37.3–62.1)</td>
<td>.017*</td>
</tr>
<tr>
<td>PA ejection time (ms)</td>
<td>138 (124–167)</td>
<td>150 (131–180)</td>
<td>.049*</td>
</tr>
<tr>
<td>PA acceleration time/ejection</td>
<td>0.28 (0.23–0.40)</td>
<td>0.32 (0.25–0.40)</td>
<td>.36</td>
</tr>
<tr>
<td>Left atrial diameter (cm)</td>
<td>2.67 (1.88–4.91)</td>
<td>2.4 (1.96–5.14)</td>
<td>.19</td>
</tr>
<tr>
<td>Left atrial diameter/aortic root</td>
<td>1.59 (1.18–2.61)</td>
<td>1.75 (1.17–2.58)</td>
<td>.64</td>
</tr>
<tr>
<td>LV diastolic diameter (cm)</td>
<td>3.50 (2.40–6.60)</td>
<td>3.26 (2.49–6.40)</td>
<td>.37</td>
</tr>
<tr>
<td>LV systolic diameter (cm)</td>
<td>1.54 (1.20–4.37)</td>
<td>1.39 (1.02–4.26)</td>
<td>.02*</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>50.2 (32.4–65.2)</td>
<td>54.9 (33.5–64.4)</td>
<td>.31</td>
</tr>
<tr>
<td>LV shortening area (%)</td>
<td>62.4 (46.6–76.6)</td>
<td>69.1 (49.8–79.9)</td>
<td>.04*</td>
</tr>
</tbody>
</table>

Values presented as median (range).
*P < .05 significant.
LV, left ventricular; PA, pulmonary artery.
the study. The long interval (3 months) between the initial and final visit may have affected owner’s perceptions of their dog’s baseline behavior. Allowing the owner to review their pet’s previous FETCH questionnaire results may have aided recall.

Normal M-mode LA size is close to the aortic root size in healthy dogs, with an upper reference range of 1.13. As expected with the remodeling and resultant LA enlargement that occurs in chronic mitral regurgitation, all of the study dogs had a left atrium to aortic root ratio (LA/Ao) ratio > 1.13 at baseline. An LA/Ao ratio > 1.7 has been demonstrated to be one of the most important independent predictors of cardiac-related death in dogs. At baseline, 5 dogs had an LA/Ao ratio > 1.7. There was no significant change in either the short-term or long-term comparison in either the size of the left atrium or the LA/Ao ratio, in contrast to another published study examining the effects of pimobendan therapy. If pimobendan exerts its effects by decreasing LA filling pressure, the lack of significant change in the size of the left atrium or the LA/Ao ratio may be a reflection of small sample size. Alternatively, a decrease in LA size may occur only with a large decrease in LA pressure or pimobendan could be decreasing the PHT by another mechanism.

Doppler-derived systolic time intervals of pulmonary artery flow have been studied in dogs with naturally occurring PHT. Several veterinary studies have demonstrated decreased right ventricular acceleration time and decreased acceleration time-to-ejection time ratios in dogs with PHT compared with normal. At baseline, our study dogs revealed decreased median acceleration times and decreased median acceleration time-to-ejection time ratios compared with published normal reference ranges. At day 91, both the pulmonary artery acceleration and ejection times had increased significantly. This observation may be indicative of an effect of pimobendan on the precapillary vasculature.

There was a decrease in the vertebral heart score in the short-term comparison, which has been noted in other studies. However, the reduction in the vertebral heart score was not maintained long term, possibly due the progressive nature of mitral valve disease.

Several limitations of this study must be acknowledged. The most important limitation was the low number of cases enrolled, particularly those with precapillary PHT. However, the 2 dogs diagnosed with precapillary PHT had either minimal change, or worsening of their results by day 91. Failure to maintain long-term improvements in NT-proBNP and quality-of-life scores may be because no actual change occurred, or there was inadequate power to detect a difference. Additionally, this study population had many different concurrently prescribed medications, which may be confounding variables. Furosemide and angiotensin converting enzymes inhibitors, however, were background therapy in all dogs.

The crossover study design allowed each patient to act as its own control during the short-term phase, minimizing intersubject variability. However, bias might have been introduced during the open-label phase. Ideally, a larger number of study subjects and a blinded long-term placebo-controlled phase should have been used. Also age and breed matching would have strengthened the comparison of the study dogs to the normal controls. ECG data did not identify any trends with pimobendan treatment. However, a more thorough evaluation of heart rate or development of arrhythmias would have required multiple 24-hour ambulatory ECG analyses. An additional limitation of this study was the lack of an echocardiographic validation study evaluating the main observer’s (KJA) inter- and intraday variability.

In conclusion, this study showed that pimobendan significantly decreased the severity of PHT in MVD as estimated noninvasively using peak TRFV. This was demonstrated in the short-term comparison with placebo, and long term comparing baseline TRFV to values at completion of the study. Pimobendan may be a viable first line or adjunctive treatment option for dogs with PHT secondary to mitral valve disease.

Footnotes

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References


